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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/394,265	09/10/1999	DAVID E. WOLF	04037/007001	3962

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	18

DATE MAILED: 12/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/394,265	WOLF, DAVID E.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's response filed 9/30/02 in Paper No. 17 is acknowledged. Currently, claims 1-17 are pending and are under examination.

New Matter

Specification

2. The amendment filed 9/30/02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: incorporation by reference to the amino acid sequence data in Edelman et al., 1972, Proc. Natl. Acad. Sci. USA, 69: 2580-4; Wang et al., 1975, J. Biol. Chem., 250: 1490-1502; and Cunningham et al., 1975, J. Biol. Chem., 250: 1503-12.

Applicant is required to cancel the new matter in the reply to this Office Action.

3. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory

material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 6 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record or reiterated as follows.

Claim 6 is indefinite in reciting, "the concanavalin A contains a mutation at one or more of the following amino acid positions: 87-90, 136-139, and 175-178" because it does not specifically recite an amino acid sequence that defines the context of the claimed concanavalin A. Further, claim 6 is indefinite in failing to designate an amino acid sequence identifier, i.e. SEQ ID Number, for the structure encompassing the claimed concanavalin A.

Lack of Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-17 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, for reasons of record or reiterated as follows.

The specification fails to provide adequate written description for the claimed genus of recombinant reduced valency carbohydrate binding ligands (CBLs) because it does not disclose representative species encompassing fragments and analogs including mutagenized residues or defined mutations at specific amino acid positions, and described by structure, physical or chemical characteristics, function correlated with structure, or a combination of each aforementioned, sufficient to establish that the applicant had possession of the claimed invention. See the Interim Guidelines on Written Description (Fed Reg , June 15, 1998, Volume 63, Number 114, pages 32639-32645). The instant specification does not contain a written description of each recombinant reduced valency CBL for use in a method of evaluating a carbohydrate, in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Adequate written description requires more than a mere statement of requisite use of recombinant reduced valency CBLs as part of the invention and a reference to a potential method of making it. The nuclei acid itself is required. See Fiers v. Revel, 25

USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

While the specification at pages 23-24 contemplates that the recombinant reduced valency CBL "can be subunits of a multimeric molecule in which the subunit has been modified, e.g. by mutation, such that the subunit does not form the normal multimer" by virtue of one or more alterations in its amino acid sequence and that the subunits of a multimer should not assemble into tetramers, the specification fails to describe and define specific structures for these multimeric molecules upon which one or more specific alterations, by mutagenesis, in the specific amino acid sequence is effected. While the specification contemplates mutagenizing concanavalin A at specific one or more amino acid positions, i.e. 87-90, 136-139, and 175-178, the specification fails to describe the specific amino acid sequence defining the structure of concanavalin A upon which the specific positions are mutagenized. The specification only described specific sites for mutation of an exemplified crystal structure of concanavalin A (page 27). The specification does not disclose representative species of fragments and analogs described by structure, physical or chemical characteristics, function correlated with structure, or a combination of each for the claimed multimeric molecules and further does not contain a written description of each recombinant reduced valency CBL for use in a method of evaluating a carbohydrate, in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing. Possession may be shown by describing the invention with sufficient relevant teaching and identifying the

characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

Enablement

6. Claims 1- 17 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record or reiterated as follows.

Enablement requires that the specification teaches those in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method of evaluating carbohydrate in a sample by combining recombinant reduced valency carbohydrate binding ligand (CBL) with a glycoconjugate and a sample having carbohydrate therein wherein the concentration of carbohydrate in the sample is indicated by the extent to which the recombinant reduced valency CBL binds the glycoconjugate.

The state of the prior art- the prior art of record fails to disclose a method that uses reduced valency CBL, i.e. trimeric conA, dimeric conA, or monomeric CBL, in a method for determining the concentration of carbohydrates by reacting the reduced valency CBL with a glycoconjugate and the carbohydrate wherein the concentration of carbohydrate is indicated by the extent to which the reduced valency CBL binds the glycoconjugate. The reduced valency CBL and the glycoconjugate bind reversibly; thus, the amount of carbohydrate is quantitated by determining the extent to which the carbohydrate occupies the reduced valency CBL or displaces the glycoconjugate from the reduced CBL.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed recombinant reduced valency structures of CBL specifically have the active epitopic sites that can bind any one of carbohydrates including monosaccharides, disaccharides, polysaccharaides, glucose, or glycoprotein and glycoconjugate reversibly, so as to allow quantitation of the amount of carbohydrate in a given sample as claimed.

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed method to use a recombinant reduced valency CBL mutagenized at specific amino acid positions, i.e. 87-90, 136-139, and 175-178, from a specific structure of concanavalin A exemplified by Reeke et al. which appears to be incorporated in the specification by reference. However, the specification fails to provide any guidance in providing the specific structure of the concanavalin A as used by Reeke et al. so as to be mutagenized at the specific amino acid positions as recited

in claim 6. Further, the specification fails to provide guidance in obtaining the specific structure of any concanavalin A or any other CBL such as lectin which are oligomeric proteins and which exist as tetramers or dimers, so as to be mutagenized at certain specific amino acid positions in the given structures, and make recombinant reduced valency CBL that is capable for use in determining the concentration of carbohydrates by properly isolating the active epitopic sites that can bind any one of carbohydrates including monosaccharides, disaccharides, polysaccharaides, glucose, or glycoprotein and glycoconjugate reversibly, so as to allow quantitation of the amount of carbohydrate in the given sample as claimed.

The presence or absence of working examples- there are no working examples provided in the specification that show how to make the recombinant reduced valency CBL or recombinant reduced valency concanavalin A from a broad genus of CBLs such as lectin and concanavalin A, having various different structures and amino acid sequences and mutagenized at specific amino acid positions for relevant use in a method of determining the concentration of carbohydrates in a given sample by reacting the resultant recombinant reduced valency CBL with any one carbohydrate and glycoconjugate, and allow quantitation of the amount of carbohydrate in the given sample as encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method of evaluating carbohydrate in a sample by combining any and all recombinant reduced valency CBL with a glycoconjugate and a sample having carbohydrate therein wherein the concentration of carbohydrate in the sample is indicated by the extent to which the recombinant reduced valency CBL binds the glycoconjugate.

The specification broadly describes as part of the invention recombinant reduced valency CBLs (see pages 29-30). The specification discloses expressed CBLs but the over all structure of the molecules encompassing the broad genus of different CBLs is not taught. The now claimed CBL recites a genus claim encompassing recombinant reduced valency CBL, which while being enabling in and of itself, is not enabled for species drawn to analogs, fragments, or variations of the CBL structure, having a specific binding site and activity for carbohydrate for use in a method of evaluating carbohydrate concentrations as required by the claimed invention. A representative number of species have not been described or defined by sufficient relevant identifying characteristics, such as function correlated with structural characteristics, including mutation at specific amino acid positions, isolation of the relevant binding sites. Thus, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable the claimed method for making and using any and all recombinant reduced valency CBL in a

method of determining the concentration of CBL, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work in any recombinant reduced valency CBL, other than the recombinant reduced valency concanavalin A obtained from the concanavalin A structure taught by Reeke et al. which is incorporated in the specification by reference and mutagenized at amino acid positions 87-90, 136-139, and 175-178; 3) there is no proper guidance that shows that any and all recombinant reduced valency CBLs would provide specific binding activity for any carbohydrates in the instant specification, 4) the nature of the invention is a method of evaluating carbohydrate in a sample by reacting recombinant reduced valency CBL with a glycoconjugate and the sample containing carbohydrate wherein the concentration of carbohydrate in the sample is indicated by the extent to which the recombinant reduced valency CBL binds the glycoconjugate, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows that any recombinant reduced valency CBL can be mutagenized at any position, to obtain one that specifically binds carbohydrates and glycoconjugate reversibly, in allowing quantitation of the amount of carbohydrate in a given sample as claimed, and lastly 7) the claims broadly recite a method of evaluating carbohydrate concentration in a sample using any recombinant reduced valency CBL obtained from mutagenizing CBLs, i.e. lectins and concanavalin A, without specifically teaching and describing these structures and without specifically stating which amino acid positions are mutagenized in each

individual CBL, so as to obtain relevant recombinant reduced valency CBL for use in effectively performing the claimed method, without undue experimentation.

Alternatively, the incorporation of essential material in the specification by reference to a publication, i.e. Reeke et al. to exemplify the structure of recombinant reduced valency concanavalin A, is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Sequence Compliance

7. It remains noted that claim 6 of the instant application recites mutagenizing concanavalin A at specific amino acid positions. The M.P.E.P., Section 2422.02, 37 CFR 1.821(b) requires exclusive conformance, with regard to the manner in which proteins having a specific nucleotide/amino acids are presented and described, with the sequence rules for all applications that include nucleotide sequences that fall within the definitions. When a sequence is presented, regardless of the format or the manner of the presentation of that sequence, the sequence must be included in a Sequence Listing and a sequence identifier ("SEQ ID NO:X") must be used. It does not appear that an amino acid sequence and its sequence identifier that defines concanavalin A as

complete and containing mutation in specific amino acid positions for use in evaluating carbohydrate in a sample, is in a Sequence Listing. APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R. 1.821-25. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

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Response to Arguments

8. Applicant's arguments filed 9/30/02 have been fully considered but they are not persuasive.

A) Applicant argues that the claims are definite in light of the amendment made to the specification, i.e. incorporation by reference ..., which makes reference to the concanavalin A defined by an amino acid sequence used by Reeke et al.

In response, the amendment made to the specification introduced new matter into the specification by incorporating by reference to the amino acid sequence data in Edelman et al., 1972, Proc. Natl. Acad. Sci. USA, 69: 2580-4; Wang et al., 1975, J. Biol. Chem., 250: 1490-1502; and Cunningham et al., 1975, J. Biol. Chem., 250: 1503-12, which include information not previously disclosed in Applicant's specification in the originally filed application. Applicant has been required to cancel the new matter in the reply to this Office Action. Additionally, the incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is deemed improper because the amendment was not accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

B) Applicant argues that the specification provides adequate written description because the claims only recite a "recombinant reduced valency CBL" which is defined in the specification as "ligands which have been genetically engineered to have less that the normal valency in page 23, lines 24-25. Applicant specifically argues that a representative number of species which is representative of the entire genus such as set forth in Table 1 on pages 25-26 provides adequate written description for representative lectins from 11 different species. Applicant argues that contrary to

Examiner's assessment, none of the pending claims recite a fragment or analog of recombinant reduced valency CBL.

In response, while the specification provides a written description of a representative species, i.e. lectin, of the claimed genus of recombinant reduced valency CBLs, it does not disclose or describe by structure and amino acid positions, the representative species having a full sequence of the structure upon which the recombinant reduced valency CBL is mutagenized, so as to define the residues that participate in dimer-dimer interactions to produce dimers which do not assemble into tetramers, so as to sufficiently establish that the applicant had possession of these claimed fragments and analogs.

While the specification at pages 23-24 contemplates that the recombinant reduced valency CBL "can be subunits of a multimeric molecule in which the subunit has been modified, e.g. by mutation, such that the subunit does not form the normal multimer" by virtue of one or more alterations in its amino acid sequence and that the subunits of a multimer should not assemble into tetramers, the specification fails to describe and define specific structures and amino acid sequences for these multimeric molecules upon which one or more specific alterations, by mutagenesis in specific amino acid positions, is effected. Alternatively, while the specification contemplates mutagenizing concanavalin A at specific one or more amino acid positions, i.e. 87-90, 136-139, and 175-178, the specification fails to describe the specific amino acid sequence defining the structure of concanavalin A upon which the specific positions are

mutagenized. The specification only described specific sites for mutation of an exemplified crystal structure of concanavalin A (page 27).

C) Applicant argues that the disclosure, as filed, is fully enabled for a method of evaluating a carbohydrate in a sample using recombinant reduced valency CBL and points to Tables II and III of the specification which discloses residues important in multimerization of concanavalin A. Specifically, Applicant argues that the specification meets all the requirements set forth to render the scope of the claimed invention fully enabled, i.e. the specification has a high level of predictability based on disclosure of residues important in multimerization of conA, the specification provides an abundance of guidance for producing recombinant reduced valency CBL and reducing the number of subunits to reduce the number of carbohydrate binding sites, working examples are not required in the specification to exemplify expression of mutated sequence and to screen recombinant reduced valency CBLs for reduced carbohydrate binding, and the specification fully encompasses the breadth of the claimed invention.

In response, Applicant's disclosure is not enabled absent any teaching, guidance, and working examples exemplifying residues or amino acid positions that are important in multimerization of any and all recombinant reduced valency CBL, other than concanavalin A. Additionally, the complete defined structure or amino acid sequence of concanavalin A and the broadly defined recombinant reduced valency CBL in claim 1, is not defined in the specification so as to establish the mutagenized residues that participate in dimer-dimer interactions.

9. For reasons aforementioned, no claims are allowed.

10. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gail Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gail Gabel
Patent Examiner
Group 1641

Christopher L. Chin

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12/15/02